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DISSEMINATED BACILLE CALMETTE-GUÉRIN INFECTION: THREE RECENT CANADIAN CASES

In Canada the principal means of tuberculosis (TB) control includes skin testing of persons at risk, pre-emptive treatment of those with asymptomatic infection, and supervised treatment of those with active disease. Routine administration of Bacille Calmette-Guérin (BCG) vaccine to infants is limited to communities where high rates of TB persist, such as certain Aboriginal communities[1]. A live bacterial vaccine, BCG should not be administered to persons with immune system impairment[1,2]. In such individuals, BCG may disseminate from the injection site to multiple organs, usually with fatal consequences[3,4]. A difficulty in observing this contraindication is the fact that congenital immunodeficiencies are usually not apparent for several months after birth because of the temporary protection afforded to such infants by maternally-derived immunoglobulins. However, such disorders are thought to be rare.

The 11 pediatric centres that participate in the Immunization Monitoring Program, Active (IMPACT), a hospital-based surveillance system[5] for immunization-related adverse events, have detected three deaths associated with immunization since surveillance began in 1991. Each instance involved BCG vaccine given to Aboriginal infants. This report summarizes the three cases.

Case 1

This female infant was born in Manitoba in May 1993. The pregnancy and newborn period were normal. The infant was given BCG vaccine at 3 days of age. She became ill at 11 weeks of age while her family was visiting Vancouver. She was being treated at the time for oral thrush which had been present for 1 month. She had fever and pyuria at presentation to British Columbia's Children's Hospital, and was admitted for treatment of urinary infection and possible sepsis. Urine and blood cultures were subsequently positive for *Enterobacter* spp. and *Escherichia coli*. Despite treatment which controlled her infection, her condition deteriorated over the following 2 weeks. The BCG vaccination site became inflammed and persistently drained serous fluid. Multiple, pea-sized subcutaneous nodules developed over her lower back and abdomen. Her liver and spleen grew in size, and hepatic function deteriorated. Pancytopenia developed, requiring multiple transfusions of platelets and packed red cells. Granulomatous chorioretinal lesions were noted and increased in number over several days.

Biopsies were performed of the BCG site and a subcutaneous nodule, both of which contained acid-fast bacilli and grew *Mycobacterium bovis*, var BCG, as identified by the provincial laboratory in British Columbia. The organism was also grown from a blood culture and a cerebrospinal fluid sample; the latter was taken because a computed tomography brain scan showed multiple nodules in both cerebral hemispheres. The cerebrospinal fluid sample contained large numbers of acid-fast bacilli.

Treatment for presumed disseminated BCG infection was started about 13 days after admission to hospital and consisted of isoniazid, rifampin, and pyrazinamide. Her management was complicated by disseminated candidiasis. She died of *Xanthomonas maltophilia* sepsis after 17 days in hospital. Immunologic investigations indicated severe combined immunodeficiency of unspecified type. There was no family history of similar cases. An older sibling was histocompatible but bone marrow transplantation was not feasible in the infant's unstable condition.

Case 2

This male infant was born in Manitoba in July 1996, following a normal pregnancy and delivery. BCG was given at 3 days of age.

He was admitted to Manitoba Children's Hospital in late August with failure to thrive, persistent diarrhea, enlargement of liver and spleen, and pancytopenia. Intensive investigations revealed HIV/AIDS.

At the time of admission to hospital, the infant also had enlarged nodes in the left axilla. About 2 months later, the BCG vaccination site on his left arm became inflammed and discharged fluid. At the same time his respiratory status further deteriorated. Biopsies were taken from the lung and affected lymph nodes. A node biopsy and drainage from the BCG site grew *M. bovis*, var BCG, as confirmed by the provincial laboratory in Manitoba. The lung tissue contained multiple granulomata but was culture negative. Treatment for disseminated BCG infection consisted of isoniazid, rifampin, and clarithromycin.

The infant remained in hospital until the time of his death 5 months later. During that time he suffered from intractable diarrhea, persistent hepatitis, repeated gastrointestinal bleeding episodes associated with pancytopenia, cytomegalovirus (CMV) pneumonitis, episodic bacterial and fungal infections, and progressive encephalopathy. He died of complications of bacterial sepsis. Autopsy was not performed so the extent of BCG-related morbidity terminally is unknown.

His parents were subsequently diagnosed as having HIV infection. The mother denied any risk factors and was not tested during pregnancy.

Case 3

This male infant was born in Alberta in August 1996, following a normal pregnancy. He was well initially. BCG vaccine was administered in the left arm at 3 weeks of age. At 8 weeks of age he was seen at Alberta Children's Hospital with a brief history of cough and fever. He was found to have markedly enlarged liver and spleen, and was admitted for investigation. CMV was cultured from his urine; treatment was undertaken with ganciclovir and intravenous immunoglobulin on suspicion that the virus was responsible for his hepatosplenomegaly.

While in hospital, the infant developed enlarged left axillary nodes. At the same time, his liver enlargement increased and pancytopenia became severe, necessitating repeated platelet infusions. Excision biopsy of an axillary lymph node showed abundant acid-fast bacilli, later identified as *M. bovis*, var BCG. He was treated with isoniazid, rifampin, pyrazinamide, and clarithromycin on suspicion that he had disseminated BCG infection. However, he failed to improve and died of respiratory failure after 32 days in hospital; 17 days of anti-TB therapy took place during this time. At autopsy, *M. bovis*, var BCG, was recovered from lung tissue and numerous acid-fast bacilli were observed in bone marrow and one adrenal gland, confirming the diagnosis of disseminated BCG infection.

Immunologic investigations revealed normal numbers of T- and B-lymphocytes and related functions. A defect was detected in the interferon gamma receptors, associated with a defect in the IFNGR1 gene. Details of the infant's disorder and studies of his parents will be published separately. The parents were healthy and unrelated.

Discussion

While BCG immunization of infants affords moderate protection against extra-pulmonary TB in the event of exposure[6], it can also reveal unsuspected disorders of immune function. Effective containment of live, attenuated BCG bacilli requires intact T-lymphocyte and macrophage function. In the absence of effective host immune function, injected bacilli can proliferate unchecked and spread throughout the body. As these cases illustrate, unresolved infection at the injection site and its spread to regional lymph nodes can be early indicators of host immunodeficiency, although regional adenopathy alone is relatively common among immunocompetent children[7]. With disseminated infection, the tissues most severely affected are usually the liver, spleen, bone marrow, and lungs[3,4]. Involvement of the skin, central nervous system, and eyes is also relatively common, as occurred in Case 1. Despite the susceptibility of BCG organisms to most anti-TB medications, the response to treatment is generally poor without immune reconstitution. Massive numbers of organisms are usually evident, as illustrated by Cases 1 and 3. Concurrent infections with CMV, fungi, and bacteria often occur, adding to the challenges of patient management.

Case 1 had severe combined immunodeficiency syndrome, a classical underlying condition among BCG-related fatalities because of the severity of the immune defect. The syndrome results from a variety of rare disorders in lymphocyte and stem cell function. Too few cells were available from this case to define the specific defect. Most instances are X-linked or autosomal recessive. The incidence rate has been estimated at 1 per 100,000 live births[8], but the actual rate among Aboriginal infants is unknown. The condition is correctable by bone marrow transplants; a histocompatible sibling was available in this instance.

Case 2 had acquired immunodeficiency syndrome of HIV infection. Her course was different from the other two cases in terms of its later onset (with failing T-cell functions), slower progression, and apparent control with anti-TB medications. BCG organisms can persist at the injection site or in regional lymph nodes for extended periods and escape containment with the onset of immunodeficiency, especially in infants with rapidly progressive HIV infection[9,10]. Infants who have potentially been exposed to HIV perinatally should not be given BCG until HIV infection has been excluded; but not all who are inadvertently immunized, as was this child, develop complications[10]. Screening for HIV infection during pregnancy is advantageous for infants in terms of treatment-related reduction of the HIV infection risk and avoidance of BCG exposure in those at risk.

The immune defect in Case 3 (interferon gamma receptor defect) is also rare; however, two previous instances have been associated with disseminated BCG infection, indicating that this receptor is important in the interplay of T-helper lymphocytes and macrophages in killing intracellular bacilli. The genetic defect is recessive; gene frequency among Aboriginals is unknown.

These rare but serious adverse events have to be considered in balancing the risks and benefits of routine BCG immunization of Aboriginal infants against the likelihood of their being exposed to TB and the feasibility of other measures in minimizing exposure risks. Providers of BCG vaccine should ascertain any family

history suggestive of congenital immunodeficiency and any risk factors for HIV infection before administering the vaccine. Routine screening for HIV infection during pregnancy would assist providers in avoiding inappropriate administration of BCG vaccine to infants at risk.

Source: *D Scheifele, MD, B Law, MD, T Jadavji, MD, on behalf of IMPACT; members also include S Halperin, MD, R Morris, MD, P Déry, MD, E Mills, MD, N MacDonald, MD, E Wang, MD, W Vaudry, MD, G Délage, MD (Canadian Paediatric Society Liaison), and P Duclos, PhD (Laboratory Centre for Disease Control Liaison).*

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Editorial Comment

Vaccines by their very purpose must maintain an extremely high benefit to risk ratio. Although vaccines are not without some risk of side effects, deaths that can be ascribed to an immunization are extremely rare. When the Institute of Medicine in the United States convened an expert panel to review deaths associated with vaccines[1], participants were unable to hypothesize a mechanism, other than the complications of a live vaccine-strain illness, whereby a vaccination can directly contribute to death.

The case series presented here by Scheifele and colleagues involving infant immunization with BCG vaccine, as well as one additional case not reported through the IMPACT, illustrates that very possibility. This additional case is a female infant who was vaccinated at birth in April 1997, in the Northwest Territories. She developed disseminated BCG infection 80 days later, and was subsequently found to have a severe combined immunodeficiency. She is now hospitalized at a tertiary-care centre that participates in the IMPACT network.

All serious adverse reactions to vaccination reported in Canada to provincial public-health authorities, either through passive reporting or through IMPACT, are reviewed by the Advisory Committee on Causality Assessment[2], which was established in 1994. The committee reviewed the recent cases; it was concerned that an infrequently used vaccine was implicated in a reaction that is considered to occur in only one per one million vaccinations. It recommended publication of the case series to alert practitioners and public-health officials of the need to be continually aware of and to consider the risk and benefit of routine BCG vaccination.

In Canada, the vaccine-associated adverse events surveillance system is well developed; it has been in operation for over 10 years. With both active and passive components, as well as awareness and encouragement of the need to report adverse events by practitioners and health-care providers, it is very unlikely that additional cases exist. Nevertheless, the reporting of three cases in the last 2 years brings the total to four cases within the last 10 years, involving a vaccine administered to a birth cohort of approximately 20,000. This represents a crude reporting rate of 20 cases of disseminated disease per one million vaccinations which is far in excess of expected. This probably is an underestimate given the likelihood of incomplete vaccination coverage in the Aboriginal populations for whom it is still being administered on a routine basis. This is a risk that must be carefully examined.

As Scheifele points out, BCG vaccination is carried out in infants to prevent extra-pulmonary TB. In Canada, < 60 cases of miliary TB and < 20 cases of TB meningitis are reported each year[3]. In 1995, there were two cases of miliary TB and no cases of TB meningitis in Aboriginal infants < 4 years of age.

The effectiveness of BCG vaccination in preventing TB varies widely[4], somewhere between < 50% to > 80%. However, in children there is evidence that BCG is more effective and provides even better protection against those more severe forms of the disease (56% to 100%). Current recommendations for the use of BCG vaccine outlined in the 5th edition of the ***Canadian Immunization Guide***[5] include

- infants belonging to groups experiencing a high rate of new infections (> 1% per year) when other control measures have proven ineffective, and
- infants at high risk of intimate and prolonged exposure to persons with TB who remain potentially infectious because they are untreated or their antimicrobial therapy is potentially ineffective.

In practice, BCG vaccination has been offered to newborns in Aboriginal populations across Canada as part of their routine immunization schedule. Recently, the Yukon Territory has revised this policy in favour of one where decisions to immunize are made on an individual basis based on risk status as suggested in the ***Canadian Immunization Guide***. On the other hand, most Medical Services Branch (MSB) regions are still using BCG vaccine in their TB control programs, although this policy is currently under review. The extent to which BCG vaccine is administered varies both between and within MSB regions. For example, there is less

hesitation to administer BCG if the mother has been screened for HIV infection and is negative.

The ***Canadian Immunization Guide*** lists common reactions to BCG vaccination as skin ulceration at the injection site, inflammatory adenitis, and keloid formation in < 2% of infants. Moderately severe reactions, such as marked lymphadenitis or suppurative adenitis, occur in 0.2 to 4.0 per 1,000 vaccinees. A total of 112 cases describing various adverse events were reported to the national adverse events database from 1987 to 1997. Of the 152 reactions described in those case reports, 73% reported the formation of abscesses or lymphadenopathy of the mild or moderate severity described above. Other frequently described reactions include fever or swelling at the injection site. These represent a reporting rate of approximately 0.07 per 1,000 vaccines which, if underreporting is taken into account, may be within the expected range.

BCG vaccination is contraindicated for persons with immune deficiency diseases including HIV infection. When the incidence of such diseases is not adequately known and may remain undiagnosed, strict vaccination policy must be thoroughly reviewed. A number of questions must be asked to reduce the morbidity and mortality associated with BCG vaccine under those circumstances.

- What is the prevalence of cases of active TB in close contact with infants who are candidates for BCG vaccine?
- What is the effectiveness of BCG in preventing TB in the population at risk?
- What is the availability and effectiveness of treatment of any TB cases that may develop in those infants who have not been immunized?
- Can relevant screening programs, such as the diagnosis of HIV infection in pregnancy, help avoid vaccination of infants with immune deficiency?

Ideally, the cornerstone of TB prevention should rely on the prompt identification and treatment of active cases of TB, as well as the detection of new infections and their treatment to prevent the development of active disease. It may be time for each jurisdiction providing BCG vaccine to ask the above questions, and to determine if there are more appropriate strategies to prevent serious TB infections in childhood without resorting to vaccination of neonates.

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Announcements

SYMPOSIUM

5 June 1998
Élizabeth Bruyère Health Pavilion, Ottawa, Ontario, Canada

Joining Forces to Control Antibiotic Resistance: Community, Long-Term, and Acute Care Settings

This one-day symposium in English is sponsored by the Sisters of Charity of Ottawa Health Services.

It will be held on Friday, 5 June 1998, from 8:00 a.m. to 4:00 p.m. at the Élizabeth Bruyère Health Pavilion, 43 Bruyère Street, Ottawa, Ontario. The registration fee is $55.00, and the final registration date is Friday, 22 May 1998.

For registration and further information, contact **Betty Waterman, Carleton Place and District Memorial Hospital, 211 Lake Avenue East, Carleton Place, Ontario K7C 1J4; telephone (613) 257-2200; FAX (613) 257-8849**.

INTERNATIONAL TRAINING COURSE IN EPIDEMIOLOGY

8 September to 18 December 1998
Paris, France

The twenty third International Training Course in Epidemiology in French on methods for the control of communicable diseases will take place in Paris from 8 September to 18 December 1998.

The aim of the course is to train all participants to analyze the epidemiological situation in their countries; and to plan, reorient, strengthen, and evaluate measures for the control of communicable diseases, in their present professional positions and in the context of the national health policy, with a view to reducing the extent of these problems in their country. The course is therefore intended for physicians or technical health personnel (nursing, veterinary, or sanitary engineering personnel), who have or will have responsibilities at the central or middle levels in their country's health programme.

There will be not more than 20 places available and applications should be received by 1 July 1998. The registration fees amount to US $6,800 (FF 32,500.–). Further information is available on request from: **CIELF Secretariat, 44, chemin de Ronde, 78116 Le Vésinet Cedex, France; telephone 01 34 80 24 64; FAX 01 34 80 24 48**.

INTERNATIONAL TRAVEL AND HEALTH
Vaccination Requirements and Health Advice

The 1998 edition of ***International Travel and Health*** has been published in English. This booklet is addressed to national health administrations and to the practising physicians, tourist agencies, shipping companies, airline operators, and other bodies who are called upon to give health advice to travellers.

In addition to summarizing the vaccination requirements of individual countries, the booklet indicates the main areas where malaria transmission occurs and where *Plasmodium falciparum* is resistant to drugs. The recommended chemoprophylactic regimen is also given for each country with malarious areas.

Other chapters cover certain health hazards to which the traveller may be exposed and indicate the areas in which these hazards are most likely to occur. The booklet also recommends a number of precautions that the wise traveller should take when visiting unfamiliar place.

This booklet can be obtained from the **Publications Department, Canadian Public Health Association, 400-1565 Carling Avenue, Ottawa, Ontario, K1Z 8R1; telephone (613) 725-3769**. Price per copy is $26.66 (including postage, handling, and GST).

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